UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/461,090 | 12/14/1999 | AXEL ULLRICH | 2923-0347 | 3321 |

6449 7590 01/04/2007

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| LU, FRANK WEI MIN | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | NOTIFICATION DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 01/04/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/04/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/461,090 | ULLRICH ET AL. | |
| | Examiner | Art Unit | |
| | Frank W Lu | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40-45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. RCE filed on August 14, 2006 and the response filed on July 13, 2006 have been entered. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on July 13, 2006. The claims pending in this application are claims 40-45, 47, and 48.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 40-43, 45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 45 and 47 have a limitation "G protein mediated extracellular signal transduction pathway". Although page 2, lines 5-22 of the specification describes that the

activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, the specification fails to define or provide any disclosure to support such claim limitation. Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2, lines 7-10 of the specification argued by applicant describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, although the examiner agrees that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway" is not limit to "growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification as argued by applicant, the phrase "G protein mediated extracellular signal transduction pathway" recited in claims 45 and 47 is a new matter. In addition, applicant does not indicate which part of the specification supports the phrase "a compound which directly acts on a growth factor precursor" as recited in claim 47.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

***Response to Arguments***

In page 6, second paragraph bridging to page 8, first paragraph of applicant's remarks filed on July 13, 2006, applicant argues: (1) "[I]n addition to the disclosure pointed out in applicant's last response, applicants respectfully point out original claim 1 which contains the language 'G protein mediated signal transduction'. Original claim 3 (which refers back to claim 1) refers to an 'extracellular signal pathway'. Thus, the current claim language is supported by a combination of originally filed claims 1 and 3. This wording is also supported by the disclosure on page 2, lines 7 to 10, where it is unambiguously disclosed that the growth factor receptor is activated via its extracellular domain and thus via an extracellular mechanism. It is shown on page 10, lines 25-32 that the GPCR ligand bound activation of the growth factor receptor does not comprise the intracellular domain"; and (2) in view of MPEP § 2163.02 and 2163.07, "[A]pplicants point out that that the exact language used in the claims does not need to appear in the specification".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2, lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, although the examiner agrees that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway" is not limit to "growth-factor receptor is

mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification as argued by applicant, the phrase "G protein mediated extracellular signal transduction pathway" is a new matter.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 40-45, 47, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 44 or 45 or 47 is rejected as vague and indefinite. Although claim 44 or 45 or 47 is directed to a method for modulating a G-protein mediated signal transduction, from the method steps in the claim, it is unclear how to modulate the receptor tyrosine kinase activation by G-protein mediated signal transduction. Please clarify.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 44 and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Dong *et al.,* teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor.

Regarding claim 44, Dong *et al.,* teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of this instant application) and Dong *et al.,* teach that batimastat decreases level of EGFR tyrosine phosphorylation in the HMEC cells (see page 6238, right column and Figure 4), Dong *et al.,* disclose contacting a cell containing a receptor tyrosine kinase (ie., a HMEC cell) capable of activation by G-protein mediated signal transduction with a test compound (ie., batimastat) as recited in the claim. Since Dong *et al.,* teach that batimastat is a selective metalloprotease inhibitor that prevents EGFR ligand release (see page 6235, abstract and right column, and page 6239, right column, last paragraph) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.,* disclose a test compound (ie., batimastat) suspected to indirectly act on a ligand precursor of the receptor tyrosine kinase (ie., EGFR, by preventing EGFR ligand release) as recited in the claim. Since Dong *et al.,* teach to compare the level of EGFR tyrosine phosphorylation of the HMEC in the presence of batimastat, antagonist mAb225 or EGF (see Figure 4), Dong *et al.,* disclose evaluating G-protein mediated receptor tyrosine kinase (ie., EGFR) activation upon exposure of the cell (ie., the HMEC cells) to said test compound (ie., batimastat) as an indication of said test compound's ability (ie., with or without ability) to modulate G-protein mediated

signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction as recited in the claim.

Regarding claim 45, since Dong *et al.,* teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 45 does not require that stimulating step must be performed before contacting step, Dong *et al.,* disclose contacting a cell with a compound (ie., batimastat) which indirectly acts on a growth factor precursor (by preventing EGFR ligand such as EGF release) in a G protein mediated extracellular signal pathway as recited in claim 45. Since Dong *et al.,* teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated

(for evidence, see canceled claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) wherein said tyrosine kinase is EGFR as recited in claim 45. Since it is known that EGFR has an extracellular domain and a cell comprising EGFR has a G-protein mediated signal transduction pathway wherein EGFR activation occurs by tyrosine phosphorylation of EGFR (see the specification, page 1, last paragraph, and page 2, second paragraph), Dong *et al.*, disclose that said receptor tyrosine kinase is EGFR and said cell (ie., the HMEC cell) comprising the extracellular domain of EGFR and having a G-protein mediated signal transduction pathway wherein one or more tyrosine residues are phosphorylated based on the activation of said G-protein mediated signal transduction pathway as recited in claim 45. Since Dong *et al.*, teach that EGF is generated from its membrane-anchored precursor by one of the ADAM family of metalloproteases (see page 6235, abstract) and it is know that EGF binds to the extracellular domain of EGFR, Dong *et al.*, disclose that the extracellular domain of said receptor (ie., EGFR) is capable of binding to its receptor ligand (ie., EGF) and said ligand is generated from a precursor of said ligand (ie., the precursor of EGF) by a proteinase-dependent cleavage (ie., one of the ADAM family of metalloproteases) thereby modulating the receptor tyrosine kinase activation by G-protein mediated signal transduction as recited in claim 45.

Therefore, Dong *et al.*, teach all limitations recited in claims 44 and 45.

***Response to Arguments***

In page 8, last paragraph bridging to page 9, first paragraph of applicant's remarks filed on July 13, 2006, applicant argues that the rejection under 35 U.S.C 102 on claims 39, 40, 42-45 and 47 should be withdrawn since "in the presently claimed method, the modulator binds directly to the growth factor receptor. In contrast to the present invention, Dong uses batimastat which inhibits the metallo-proteinase".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection on claims 44 and 45 because claims 44 and 45 do not require "contacting the cell with a compound which directly binds to a growth factor precursor" as argued by applicant.

***Conclusion***

8. No claim is allowed.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

December 22, 2006

FRANK LU
PRIMARY EXAMINER